Support for the Amendments

Applicants have amended independent claims 6 and 23, and the claims dependent thereon, in order to more clearly describe and distinctly claim the subject matter of applicants' method for treating obesity and method for regulating growth and development of adipose tissue. Specifically, applicants have cancelled claims 16 and 29 and incorporated the subject matter therein into independent claims 6 and 23, respectively, to recite that the methods comprise the steps of administering to a mammal a therapeutically effective amount of an inhibitor compound to inhibit the protein-protein interactions of HMGI proteins.

These amendments to the claims are fully supported in the specification as originally filed, and thus no new matter is introduced by these amendments in accord with 35 U.S.C. Section 132. Accordingly, applicants request entry of these amendments.

Election/Restriction

The Examiner has acknowledged applicant's election with traverse of the claims of Group V, claims 6-12, 16-19, 23-25 and 29-32, on the ground(s) that the search and examination of the instant application can be made without serious burden to the Examiner because groups II, IV, VI and VII are classified in Class 435 and groups III and V are classified in Class 514. The Examiner has not found this persuasive on the basis that the groups have been classified among two major classes and are further classified in 5 different subclasses and because the divergent subject matter would require different, non-overlapping searches for each group. Accordingly, the Examiner has made the requirement final.

Oath/Declaration

The Examiner has objected to the oath or declaration and has requested a new oath or declaration. Applicant has filed concurrently herewith a new oath or declaration, and accordingly, the Examiner's objection should be withdrawn.

Specification

The Examiner has objected to the abstract of the disclosure and states that the abstract is greater than 250 words in length and needs to be reduced. Applicant has filed concurrently herewith a new abstract of the disclosure. Accordingly, the Examiner's objection to the abstract of the disclosure should be withdrawn.

Claim Rejections under 35 U.S.C. §112, second paragraph.

The Examiner has rejected the claims under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner has rejected claims 6-12 and 16-19 under 35 U.S.C. §112, second paragraph, because the Examiner states that the claims do not set forth any steps involved in the method/process and it is unclear what method/process applicant is intending to encompass. The Examiner has rejected claims 23-25 and 29-32 under 35 U.S.C. §112, second paragraph, because the Examiner states that the claims do

not set forth any steps involved in the method/process and it is unclear what method/process applicant is intending to encompass. The Examiner has rejected claims 16 and 29 under 35 U.S.C. §112, second paragraph, because the Examiner states that both claims recite "inhibiting the protein-protein interactions of HMGI proteins" (page 65, lines 24-25 and page 67, lines 5-6, respectively) but neither the claims nor the specification define "protein-protein interactions" and therefore, it is impossible to define the metes and bounds of this phrase. Applicants' claims as amended obviate the Examiner's rejections.

As set out above, applicant has canceled claims 16 and 29 and incorporated the subject matter therein into independent claims 6 and 23, respectively, to recite a method for treating obesity in a mammal, and a method for regulating growth and development of adipose tissue in a mammal, by reducing the biological activity of HMGI genes in the mammal which comprises the steps of administering to a mammal a therapeutically effective amount of an inhibitor compound to inhibit the protein-protein interactions of HMGI proteins.

Accordingly, the Examiner's rejection of claims 6-12 and 16-19 and 23-25 and 29-32 under 35 U.S.C. §112, second paragraph, should be withdrawn.

Claim Rejections under 35 U.S.C. §112, first paragraph.

Claims 6-12, 16-19, 23-25 and 29-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. Specifically, the Examiner states that the specification discloses "The reduction in biological activity of HMGI genes may be achieved by inhibiting the DNA-binding activity of HMGI

genes which may be carried out by administering to the mammal a therapeutically effective amount of netropsin, distamycin A or Hoechst 33258 (bisbenzimide)" but that the specification fails to disclose the composition in which any of the three drugs will be administered, the frequency of administration, the need for coincidental changes in behavior including diet and exercise or the effect of confounding factors such as diabetes. The Examiner asserts that since these drugs are not known in the art to reduce the *in vivo* activity of HMGI proteins, it cannot be predicted if such a reduction would occur. The Examiner notes that the specification discloses "The reduction in biological activity of HMGI genes may be achieved by inhibiting the expression of HMGI genes which may be carried out by administering to the mammal a therapeutically effective amount of an oligonucleotide which has a nucleotide sequence complementary to at least a portion of the mRNA of the HMGI gene" but that the specification has only general statements concerning the frequency, dosage, mode and site(s) of administration of antisense oligonucleotides and leaves these factors to be determined in accordance with conventional practice among medical or veterinary professionals. The Examiner points out that claim 16 recites inhibiting protein-protein interactions of HMGI proteins but that it is known that HMGI proteins regulate gene expression by functioning as architectural factors to induce conformational changes in DNA, however, the specification fails to disclose how the inhibition of protein-protein interactions of HMGI proteins would be accomplished as well as what compounds would be used to accomplish this goal. The Examiner concludes that given the unpredictability in the art, there is also a lack of a working example in the specification, specifically, there is no example of a reduction in biological activity of an HMGI protein in a mammal that is produced by either of the disclosed methods quoted above, and hence in view of the unpredictability in the arts of

treating obesity and antisense oligonucleotide technology, the lack of clear guidance with respect to dosage and frequency of administration of drugs or antisense oligonucleotides and the lack of a working example, one skilled in the art could not use the inventions of claims 6-12 and 16-19 without undue experimentation. Applicants traverse the Examiner's rejections.

Aberrations in the genetic mechanisms that control growth and proliferation have emerged as a primary event in carcinogenesis. The function of HMGI-C and HMGI(Y), two embryonically expressed DNA-binding proteins, was investigated because their expression is highly associated with tumor development. Disruptions of either HMGI-C or HMGI(Y) in humans result in a diverse array of solid mesenchymal tumors. Most prominent among these neoplasms are uterine leiomyomata, the most common pelvic tumors in women and the indication for over 200,000 hysterectomies annually in the United States. In tumors of mammary and thyroid glands as well as in prostate cancer, HMGI expression is highly correlated with tumor progression and metastasis, suggesting that these proteins can be used for as progression markers for a variety of tumor types.

Further proof for the pivotal role of HMGI proteins in both normal and pathological growth was obtained in the mouse system. Homologous recombination was used to inactivate murine HMGI-C gene. Demonstrating the importance of the HMGI genes in growth regulation, HMGI-C knockout mice exhibit significant growth retardation (mutant mice are 60% smaller than their wild-type littermates) with the reduction in most tissues commensurate with the overall decrease in the body weight. Even more importantly, these pygmy mice are highly resistant to chemically induced skin cancer. Specifically, the frequency of tumor development in the knockout mice is 40% of that in the control animals and tumor multiplicity exhibits a 20-fold decrease. Independently, inhibition of HMGI-C

synthesis was shown to render thyroid epithelial cells intransigent to retroviral transformation. At the molecular level, HMGI proteins function in transcriptional regulation by promoting cooperative binding of the transcription factors to DNA. Deregulation of the downstream target genes can easily account for the important biological roles of the HMGI proteins as well as for the dramatic consequences of their inappropriate expression.

Lipomas are one of the most common mesenchymal neoplasms in humans. They are characterized by consistent cytogenetic aberrations involving chromosome 12 in bands q14-15. Interestingly, this region is also the site of rearrangement for other mesenchymally derived tumors. The present invention demonstrates that HMGI-C, an architectural factor that functions in transcriptional regulation, has been disrupted by rearrangement at the 12q14-15 chromosomal breakpoint in lipomas. Chimeric transcripts were isolated from two lipomas in which HMGI-C DNA-binding domains (A-T hook motifs) are fused to either a LIM or an acidic transactivation domain. These results identify the first gene rearranged in a benign neoplastic process that does not proceed to a malignancy and suggest a role for HMGI-C in adipogenesis and mesenchyme differentiation.

HMGI-C is an attractive candidate gene to be implicated in lipoma formation. This gene is required in transformation (Berlingieri et al., 1995) and is a transcriptional regulatory factor as are many genes identified at translocation breakpoints in a variety of tumors (Rabbitts, 1994). Secondly, disruption of HMGI-C leads to mice of small stature which, most intriguingly, have disproportionately less body fat than normal littermates (Benson and Chada, 1994). Finally, mouse HMGI-C maps to a region syntenic to human 12q14-15 which is the area most frequently rearranged in lipomas (Mandahl et al., 1988). Therefore, the

human homolog of the mouse HMGI-C gene was cloned and its possible role in lipomas investigated.

Growth is one of the fundamental aspects in the development of an organism. Classical genetic studies have isolated four viable, spontaneous mouse mutants (Green, 1989) disrupted in growth, leading to dwarfism. Pygmy is unique among these mutants because its phenotype cannot be explained by aberrations in the growth hormone-insulin-like growth factor endocrine pathway (Lin, 1993; Li, et al., 1990; Sinha et al., 1979; Nissley et al., 1980). The present invention shows that the pygmy phenotype arises from the inactivation of HMGI-C and are critical in the assembly of stereospecific transcriptional complexes (Tjian & Maniatis, 1994). In addition, HMGI-C and the other HMGI family member, HMGI(Y)(Johnson et al., 1988), were found to be expressed predominantly during embryogenesis. The HMGI family are known to be regulated by cell cycle dependent phosphorylation which alters their DNA binding affinity (Reeves et al., 1991). Overall, these results demonstrate the important role of HMGI proteins in mammalian growth and development.

Among the most prominent characteristics consistently exhibited by cancer cells are karyotypic aberrations which disturb genes essential for the regulation of fundamental cellular processes. A wide array of solid mesenchymal tumors is characterized by recurrent rearrangements of chromosomal bands 12q13-15 or 6p21-23. This study shows that HMGI expression is normally restricted to undifferentiated, rapidly dividing cells but is activated in differentiated adipocytes following translocations of 12q13-15 or 6p21-23 in human lipomas. The present invention shows that the molecular pathway of tumor development is dictated by the precise nature of HMGI disruption and that HMGI misexpression in a differentiated cell is a pivotal event in benign tumorigenesis.

Uterine leiomyomata are the most common pelvic tumors in women and are the indication for more than 200,000 hysterectomies annually in the United States. Rearrangement of chromosome 12 in bands q14-q15 is characteristic of uterine leiomyomata and other benign mesenchymal tumors, and a YAC spanning chromosome 12 translocation breakpoints was identified in a uterine leiomyoma, pulmonary chondroid hamartoma, and lipoma. Recently, it was demonstrated that HMGI-C, an architectural factor mapping within the YAC, is disrupted in lipomas, resulting in novel fusion transcripts. This study concerns the localization of translocation breakpoints in seven uterine leiomyomata 10 to >100 kb upstream of HMGI-C by use of fluorescence in situ hybridization. These findings suggest a different pathobiologic mechanism in uterine leiomyomata from that in lipomas. HMGI-C is the first gene identified in chromosomal rearrangements in uterine leiomyomata and has important implications for an understanding of benign mesenchymal proliferation and differentiation.

Recently, molecular dissection of this chromosomal region has substantiated this hypothesis. To identify a gene at the breakpoint on chromosome 12 in uterine leiomyomata, a high-density physical map of the t(12;14) breakpoint region was constructed and identified a YAC, 981f11, that spans the translocation breakpoints in a uterine leiomyomata, pulmonary chondroid hamartoma and a lipoma. Further detailed characterization showed that the gene for HMGI-C, an architectural factor that is a non-histone component of chromatin, maps within 981f11 and is disrupted in lipomas. HMGI-C is rearranged in lipomas with chromosome 12 translocations, resulting in novel chimeric transcripts that fuse the DNA-binding A-T hook domains of HMGIC with potential transcriptional activation domains.

Accordingly, the Examiner's rejection of claims 6-12, 16-19, 23-25 and 29-32 are rejected under 35 U.S.C. 112, first paragraph, should be withdrawn.

It has been consistently held that the first paragraph of 35 U.S.C. Section 112 required nothing more than objective enablement.... In satisfying the enablement requirement, an application need not teach, and preferably omits, that which is well-known in the art.... How such a teaching is set forth, whether by the use of illustrative examples or by broad descriptive terminology, is of no importance since a specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as complying with the first paragraph of 35 U.S.C. Section 112 unless there is reason to doubt the objective truth of the statements relied upon therein for enabling support... The error we see in Staehelin's approach to the question before us is that Staehelin would require a patent specification to be a blueprint which, if followed, would unfailingly reproduce exactly an applicant's claimed invention. However, the law does not require a specification to be a blueprint in order to satisfy the requirement for enablement under 35 USC Section 112, first paragraph. *Staehelin v. Secher*, 24 U.S.P.Q.2d 1513, 1516 (B.P.A.I 1992).

In order to be entitled to the benefit thereof, it is not necessary that a patent application exactly describe the limitations of a claimed process, but only so clearly that those skilled in the art would recognize from the disclosure that applicant invented the claimed process, including those limitations. *In re Wertheim et al.*, (C.C.P.A. 1976) 541 F2d 257, 191 U.S.P.Q. 90.

In view of the foregoing response, applicant requests reconsideration pursuant to 37 C.F.R. Section 112 and allowance of the claims pending in this application. Applicant requests the Examiner to telephone the undersigned attorney

should the Examiner have any questions or comments which might be most expeditiously handled by a telephone conference.

Applicant's attorney authorizes the Examiner to charge Deposit Account 13-4822 if there are any additional fees due in connection with this response.

Respectfully submitted,
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